

Triflic Acid and Sodium Triflate as Chaotropic Mobile Phase Additives in RP-LC

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Abstract

In reversed-phase liquid chromatography (RP-LC), the retention of cationic analytes such as basic drugs is known to be enhanced by the presence of chaotropic additives in the mobile phase. In this study, the chaotropic effect of triflate anion was evaluated. Four cationic drugs were chromatographed on a C18 column, comparing retention obtained between triflate, perchlorate, and trifluoroacetate mobile phase additives in the range from 5 to 30 mM. It was found that triflate exhibited very similar chaotropic effect to perchlorate. Retention factors afforded by triflate were typically within 5% of the corresponding perchlorate values throughout the entire concentration range studied. It was also found through dynamic vapor sorption studies that sodium triflate monohydrate salt was a more stable crystalline solid than the sodium perchlorate monohydrate salt with regard to hygroscopicity, showing good stability in the range of 10–70% relative humidity compared to sodium perchlorate monohydrate which was stable only within the range of approximately 20–40% relative humidity. The better physical stability and handling properties of the sodium triflate monohydrate salt suggests it may be an attractive alternative to sodium perchlorate monohydrate salt as a chaotropic additive in RP-LC analysis of pharmaceuticals.

Introduction

Retention of analytes in reversed-phase liquid chromatography (RP-LC) is greatly affected by the presence or absence of a charged group within the molecular structure of the analyte. This principle is frequently encountered by RP-LC practitioners in the pharmaceutical industry, because many drugs are basic and become cationic at low pH (1). Analyte retention and column loading capacity in RP-LC will ordinarily be low for cationic analytes relative to neutral analytes of similar structure (2,3), but retention of cations can be enhanced by certain anionic mobile phase additives, which are often referred to as lipophilic or chaotropic additives (4,5). These additives help to overcome the general problem of poor retention of cationic analytes, and often allow useful alterations of chromatographic selectivity in separations of mixtures containing both neutral and cationic analytes

(4). The chaotropic retention mechanism is believed to occur from the ability of the chaotropic additive to disrupt the solvation shell surrounding an analyte molecule, thereby rendering it more amenable to adsorption onto the hydrophobic stationary phase. For mobile phases containing acetonitrile (MeCN) and water, chaotropic anions have also been shown to partition significantly into the adsorbed layer of MeCN which is present on the hydrophobic stationary phase surface, causing the surface to become electrically charged and providing an additional mechanism of retaining an oppositely charged analyte. Another important aspect of chaotropic additives in RP-LC is that they do not permanently alter the surface characteristics of the stationary phase, which is a distinct advantage over traditional ion pairing additives (4,5).

Mobile phase additives such as trifluoroacetate, tetrafluoroborate, perchlorate, and hexafluorophosphate possess substantial cation retaining power in RP-LC (4,6–8). The observed ranking of chaotropic anions with regard to cation retaining power appears to follow the so-called “Hofmeister series”, based on protein precipitation properties (8). Similar behavior is observed for anion exchange resins, which show relatively low affinity towards kosmotropic anions such as acetate, and high affinity towards chaotropic anions such as perchlorate (9,10). Anions possessing a high degree of chaotropicity typically have a molecular structure which allows for delocalization of the negative charge (4). This view is consistent with the presence of fluorine atoms in many of the known chaotropic anions, such as trifluoroacetate, tetrafluoroborate, and hexafluorophosphate (4,6–8). The substitution of hydrogen atoms with strongly electron withdrawing fluorine atoms will presumably have a charge delocalizing effect on the anion. The increase in chaotropicity due to fluorine is illustrated by the successive increasing affinity towards an anion exchange resin when switching from acetate to the respective mono-, di-, and trifluoroacetate analogues (11).

Interestingly, the trifluoromethanesulfonate (triflate) anion appears to have been overlooked as a potential chaotropic additive in RP-LC. In principle, triflate should afford even greater chaotropic effect than trifluoroacetate, based on the greater retention of triflate relative to trifluoroacetate on an anion exchange resin (12). The higher chaotropicity of triflate relative to trifluoroacetate is also reasonable on theoretical grounds, because three oxygen atoms allow increased delocalization of negative charge through three resonance structures for triflate,

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compared to only two for trifluoroacetate (Figure 1). These observations all suggest that triflate anion should exhibit significant chaotropic effect in RP-LC, significantly greater than trifluoroacetate, potentially making triflate a useful addition to the group of commonly used chaotropic reagents in RP-LC. Although trifluoromethanesulfonic acid (triflic acid) has been used in LC for pre-column derivatization reactions (13), for pH adjustment of mobile phases in analysis of transition metal complexes (14,15), and evaluated as a mobile phase additive for chiral separations (16) or for separation of peptides in carbon dioxide mobile phases (17), there is a lack of studies in which the cation retaining power of triflate has been compared to other commonly used chaotropic additives in RP-LC. Only one study of this type (18) was found, in which a comparison was made between triflic acid and trifluoroacetic acid (TFA) on a series of cationic oligomeric analytes. Retention of the oligomers was compared between a 0.1% triflic acid mobile phase and a 0.1% TFA mobile phase on a Zorbax SBC18 300Å column (Agilent, Wilmington, DE). Despite the slightly higher molarity of 0.1% TFA (~ 13 mM) compared to 0.1% triflic acid (~ 11 mM), the retention times of the oligomers were significantly higher for triflic acid compared to TFA, even when using a steeper solvent gradient for triflic acid relative to TFA. This suggests that triflic acid has substantially higher cation retaining power on a molar basis compared to TFA.

In the following report, the chaotropic effect of triflate relative to two commonly used chaotropic additives, perchlorate and trifluoroacetate was evaluated. Comparisons were made by preparing mobile phases containing equimolar amounts of the three different additives and comparing retention of several cationic drugs. Comparisons were made for both the free acid form and sodium salt form of the additives. The physical properties of the commercially available sodium triflate salt for comparison to sodium perchlorate salt was also investigated to see if one salt had any practical advantages over the other in terms of storage and handling properties which may be encountered in typical laboratory use.

Experimental

Water was purified using a Purelab Ultra system (Elga Labwater, Lowell, MA). MeCN and sodium perchlorate monohydrate were HPLC grade (Fisher Scientific, Fair Lawn, NJ). Sodium triflate (> 98% purity) was from TCI America (Portland, OR). All other chemicals were 99% purity or better. Thiourea, diphenhydramine (HCl salt), and acetophenone were from Acros Organics (Geel, Belgium). Pindolol was from Tocris Bioscience (Ellisville, MO). All other chemicals were from Sigma-Aldrich-Fluka (St. Louis, MO).

LC experiments were conducted using an Alliance 2695 separations module and a 2996 photodiode array detector (Waters Corporation, Milford, MA). Column was Xterra-MS C18 column of dimensions

3.0 × 150 mm, dp 3.5 μm (Waters) and maintained at 25°C. Thermogravimetric (TG) analysis and differential thermal (DT) analysis was performed using a model SSC/5200 TG-DTA instrument (Seiko Instruments Inc., Torrance, California). Dynamic vapor sorption (DVS) analysis was conducted with a DVS HT instrument, equipped with an integral digital camera for obtaining photographs of samples within the humidity controlled environment during analysis (Surface Measurement Systems, Allentown, PA). Elemental analysis was performed by Robertson Microлит Laboratories (Madison, NJ).

In order to determine the relative retaining power of the chaotropic additives, the retention of four protonated cationic analytes were measured with a C18 column, using 33% MeCN mobile phases containing several arbitrary concentrations of each additive. Model analytes were basic drugs which have been used previously in similar chromatography studies, using an acidic mobile phase to insure the analytes were in protonated form and therefore positively charged (4,7). Mobile phases were

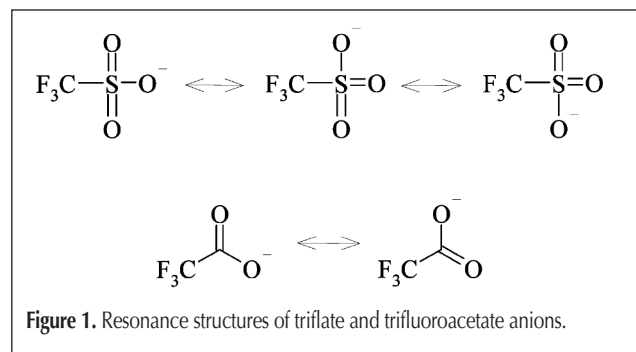
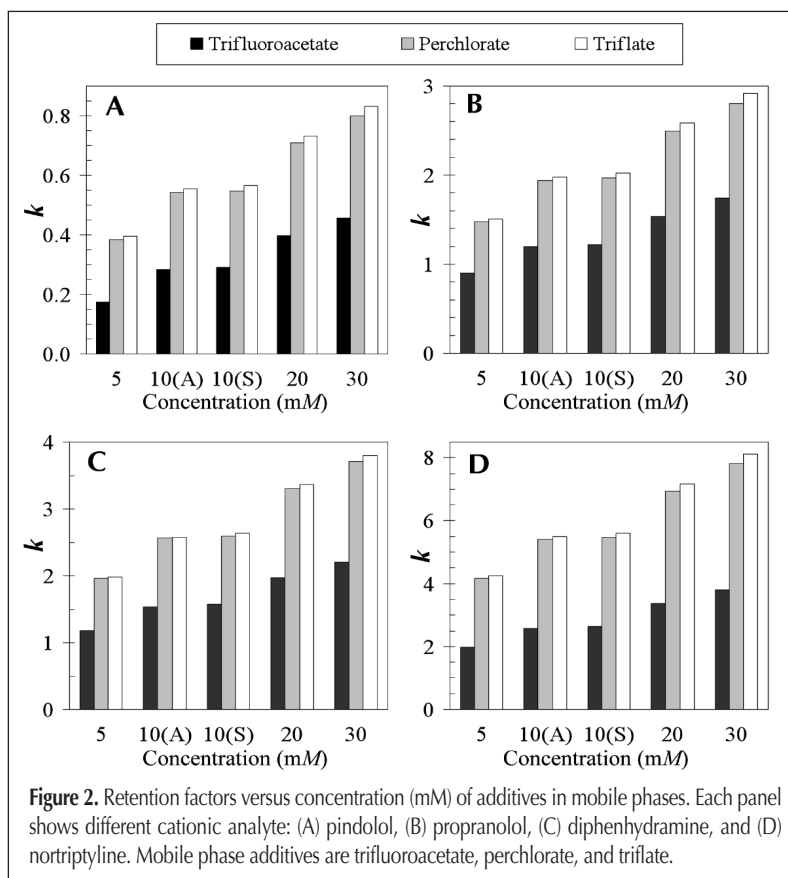


Figure 1. Resonance structures of triflate and trifluoroacetate anions.



prepared from TFA, perchloric acid, and triflic acid by dilution to the target molarity (10 mM) in the mobile phase. Similar to TFA, pure triflic acid is a dense liquid which fumes strongly in air and should be handled only in a fume hood. The actual molarity of acid in the mobile phases was carefully tested by neutralization titration with standard base to insure the accuracy of acid concentration, and double checked by pH measurement. To insure the reliability of the observed ranking of retaining power, a second experiment was conducted. In this case, retention of the same model analytes was obtained for mobile phases containing the sodium salt form of the trifluoroacetate, perchlorate, and triflate anions instead of the acid form. To insure pH control in the sodium salt mobile phases, the mobile phases were prepared in 1.8 mM phosphoric acid in 33% MeCN, which will produce a dissociated hydronium ion concentration of 1 mM (pH value of 3.0) in 33% MeCN medium (19).

Results and Discussion

Comparison of cation retaining power of triflate, perchlorate, and trifluoroacetate

The results of the chromatographic experiments are shown in Figure 2, which shows the retention factors obtained with 5, 10, 20, and 30 mM concentrations of each sodium salt additive, along with the retention factors obtained for mobile phases containing 10 mM of each acid. Figure 3 shows example chromatograms of the four model cationic analytes in the three different 10 mM acid mobile phases. In all cases, triflate produced very similar retention relative to perchlorate, always affording a slightly higher retention factor than perchlorate under each anion concentration. The chromatographic effi-

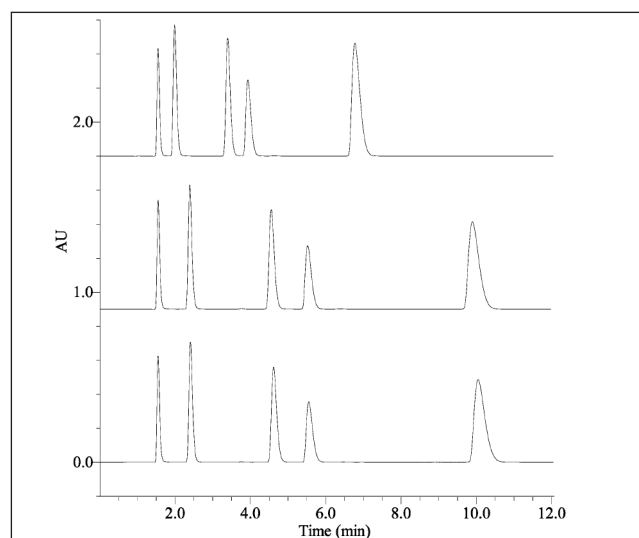


Figure 3. Effect of three chaotropic additives on retention of model cationic analytes. Chromatograms (UV 210 nm) are obtained with 33% MeCN mobile phases containing 10mM of (bottom to top) triflic acid, perchloric acid, and TFA. Elution order of peaks is thiourea, pindolol, propranolol, diphenhydramine, and nortriptyline. 1 μL injection was made of solution containing 0.2 mg/mL of diphenhydramine and nortriptyline, and 0.1 mg/mL of other compounds. Flow rate was 0.5 mL/min.

ciency afforded by triflate was also very similar to perchlorate, based on similar USP plate counts (typically less than 5% change when switching between perchlorate and triflate). Although triflate and perchlorate afforded very similar retention to each other, both afforded substantially more retention relative to trifluoroacetate, which is in accord with other studies comparing cation retaining power of perchlorate and trifluoroacetate (4,6–8,20). A neutral compound, acetophenone, was also injected under each mobile phase condition and showed no significant change in retention ($k = 2.23 \pm 0.02$) under any of the mobile phase conditions, indicating that the chaotropic reagents were influencing only the charged compounds but not neutral ones, which is also in accord with other studies (7,8). Thus, these experiments indicate that triflate ion appears to have a chaotropic effect in RP-LC very similar to perchlorate, based on the observed retention of all four model cationic analytes.

In light of the similar chromatographic behavior of the perchlorate and triflate salts, other aspects of these two salts were considered, in particular the handling properties under typical laboratory conditions, which might give a practical advantage of one salt over the other salt as discussed in the following sections.

Physical properties of sodium triflate salt

Sodium triflate is known to exist as both anhydrous and monohydrate crystalline forms (21,22). The commercially supplied sodium triflate salt used in the experiments was obtained in anhydrous form. DT analysis indicated the onset of a thermal event at 253°C followed closely by a second thermal event at 256°C (Figure 4). This is in good agreement with a reported study on the crystal structure of anhydrous sodium triflate, for which a phase transition was observed at 252°C followed closely by melting at 259°C (21). The anhydrous sodium triflate salt was very hygroscopic. When samples of the material were exposed to the laboratory atmosphere [55% relative humidity (RH), 20°C], the material gained weight rapidly, due to adsorption of water from the air. Upon overnight exposure, the observed weight increase of approximately 10% corresponded closely to the theoretical weight of one stoichiometric equivalent of water (theoretical weight increase 10.47%). The material thus produced was subjected to TG analysis, and showed a loss on drying of 9.4%, in excellent agreement with the 9.48% theoretical weight percent

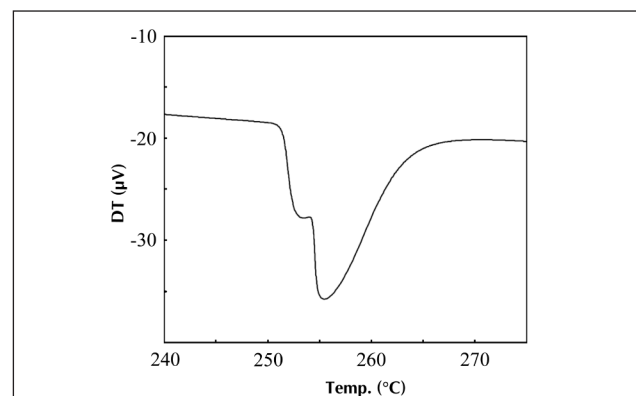


Figure 4. DT analysis of anhydrous sodium triflate salt in temperature range of 250–275°C (heating rate 7.5°C/min, showing phase transition and melting events at temperatures of 253°C and 256°C).

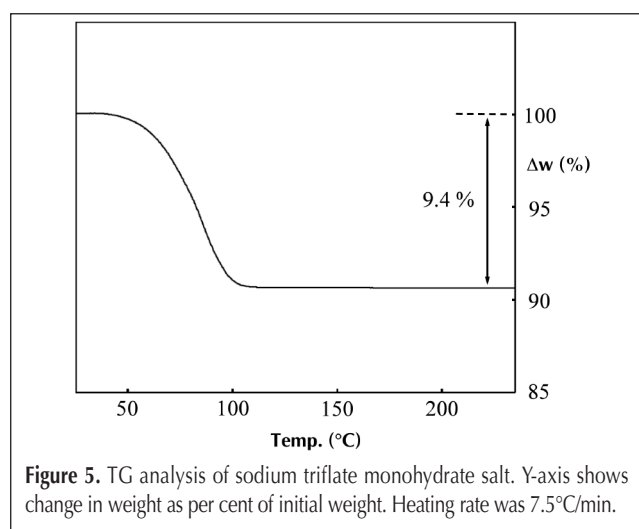
of one equivalent of water in the monohydrate form (Figure 5). Elemental analysis (two replicates) of the experimentally produced monohydrate also showed excellent agreement with calculated percent w/w values for a theoretical monohydrate (Calculated for $\text{NaCF}_3\text{O}_3\text{S H}_2\text{O}$: C, 6.32; H, 1.06; F, 29.99; S, 16.87. Found: C, 6.41,6.32; H, 1.07,1.03; F, 30.36,30.34; and S, 16.50, 16.66).

To determine the RH limits in which the sodium triflate monohydrate salt was stable, DVS analysis was conducted (Table I). Reducing the humidity from an initial value of 50% RH to 10% RH caused almost no loss in weight (0.02%). When humidity was reduced further from 10% to 0% RH, a decrease in weight occurred, eventually reaching constant weight after a change of 10.36% (relative to the final weight), again indicating the loss of one equivalent of water. Increasing the humidity back up to 10% caused re-hydration to occur, indicating that the process was reversible. Humidity could be increased from 10% RH to as high as 70% RH with minimal change in weight (0.12% increase from 10% to 70% RH). This process could be repeated through a second desorption–adsorption cycle, showing the same behavior, indicating that the material was physically stable within the limits of 10–70% RH (Table I). Only when exposed to humidity above 70% did the material begin to deliquesce. Thus, there appears to be a fairly wide range of humidity in which the sodium triflate monohydrate is physically stable, unlike the anhydrous form which gains moisture even at relatively low humidity levels (10% RH).

Table I. Adsorption Isotherms Obtained for Sodium Triflate Monohydrate During DVS Analysis*

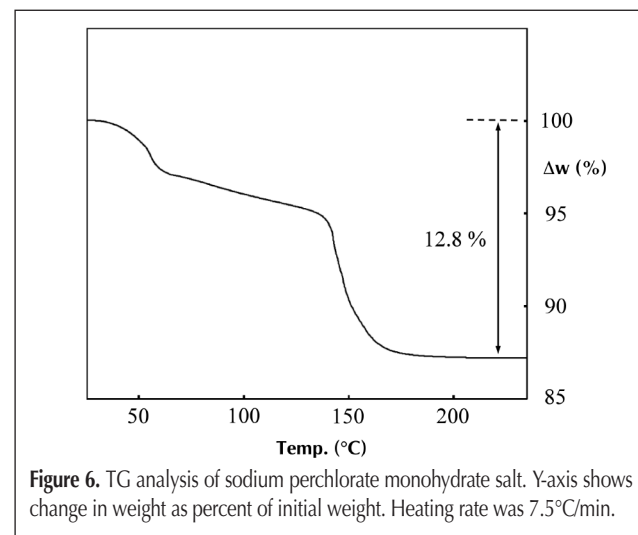
Rel. Humidity %	0	10	30	50	70
Desorption 1	0	10.36	10.38	10.38	–
Adsorption 1	0	10.35	10.37	10.38	10.47
Desorption 2	–0.03	10.38	10.39	10.40	10.47
Adsorption 2	–0.03	10.34	10.37	10.38	10.47
Desorption 3	–	–	–	10.41	10.47

* First desorption cycle was started at 50% RH (similar to the ambient humidity level in laboratory). Analysis was conducted at 25°C, each step held for 2 h except for 0% RH and 10% RH steps which required 6 h until constant weight was obtained. Values are expressed as percent change relative to dry weight.



Physical properties of sodium perchlorate salt

Sodium perchlorate has long been known to exist in both anhydrous and monohydrate crystalline forms (23). The sodium perchlorate salt used in this study was the commercially supplied monohydrate form. The 12.8% weight loss observed during TGA analysis (Figure 6) showed excellent agreement with the theoretical weight of one equivalent of water (12.83%). However, the perchlorate monohydrate was not physically stable under ambient conditions in the laboratory. Although weight gain was slow, deliquescence could be observed after overnight exposure. The same behavior occurred under controlled 25°C/50% RH conditions using the DVS instrument, showing an increase in weight of approximately 5% after 2 h at 25°C/50% RH conditions. When the humidity was lowered to 40% RH, the material appeared to be stable and no change in weight was observed. A second DVS experiment was therefore conducted using 40% RH as the initial value. The observed DVS analysis result is shown in Figure 7. It was found that humidity could be decreased successively to 30% and 20% RH with minimal weight loss (Figure 7A–7B). Decreasing further to 10% RH (Figure 7C) caused almost all of the water to be lost. Indeed, after 6 h at 10% RH the sample weight was still decreasing slowly, indicating that all of the water would likely have been lost at 10% RH with sufficient time. Upon further decrease of humidity to 0% RH (Figure 7D), constant weight was achieved after approximately 1 h. The total weight change from initial weight to dry weight was 14.65% (relative to the dry weight), which corresponds well to the theoretical 14.72% value for the weight of one mole of water relative to anhydrous sodium perchlorate. When increasing humidity stepwise to 10% RH (Figure 7E) and then from 10% to 20% RH (Figure 7F), no weight gain was observed. Increasing further from 20% to 30% RH (Figure 7G) showed a small weight gain, and the weight appeared to be reaching a plateau but was still increasing after 6 h (1.32% increase relative to dry weight). Increasing humidity from 30% to 40% RH (Figure 7H) showed another increase in weight, also appearing to approach a plateau but not yet reaching a constant value after 6 h. The observed weight increase of 2.91% (relative to dry weight) after 6 h at 40% RH was only a small fraction of the amount corresponding to one mole of water. Increasing humidity further from 40% to 50% RH



(Figure 7I) caused a more rapid weight gain which continued at an almost constant rate for 6 h showing no sign of reaching a plateau, and deliquescence on the surface of the solid was observed.

Unlike the triflate salt which remained as a white powder during the DVS analysis, the physical appearance of the perchlorate salt changed significantly from the initial state to the dried state, becoming a white opaque solid which resembled a sintered material, in contrast to the large transparent crystals of monohydrate material prior to drying (Figure 8), which has been noted by others (24). The appearance of the dried material remained unchanged upon increasing humidity until 50% RH was reached, when signs of deliquescence could be observed on the surface of the solid after being exposed to the 50% RH (Figure 8). No attempt was made to characterize the dried solid, which could be either amorphous solid or one of several known crystalline forms of anhydrous sodium perchlorate (25). Even though the exact physical nature of the dried material was not determined, these experiments suggest that it is easy to remove the water from sodium perchlorate monohydrate by simply reducing humidity to below 20% RH, but once the material is dried it did not appear feasible to re-generate the monohydrate through the simple manipulation of humidity level.

Comparison of handling properties of sodium perchlorate versus sodium triflate

The sodium perchlorate and sodium triflate salts have several similarities. Both salts can exist in either anhydrous or monohydrate forms. The anhydrous forms are very hygroscopic. The monohydrate forms can be easily dried by either heating or simply storing in a dry atmosphere. However, there are important differences which were found between the monohydrate forms of sodium perchlorate and sodium triflate. The perchlorate monohydrate was stable under a rather narrow humidity range of 20–40% RH, and regeneration of monohydrate from

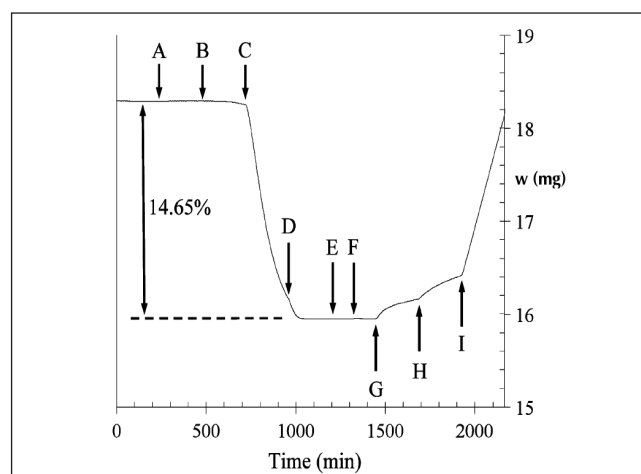


Figure 7. DVS analysis of sodium perchlorate monohydrate salt showing weight of sample (w) versus time, and humidity is decreased in stepwise fashion to 0%RH, followed by stepwise increase to 50% RH. Initial condition was 40% r.h followed by changes to 30% (A), 20% (B), 10% (C), 0% (D), 10% (E), 20% (F), 30% (G), 40% (H), and 50% (I). Each condition was held for 6 hr except for the 10 and 20% RH levels during the increasing humidity portion of the experiment (2 h). Temperature was constant at 25°C.

anhydrous material by exposure to a specific humidity level does not appear to be a practical option. This is in contrast to the triflate monohydrate, which was stable over a much wider range of humidity (10–70% RH) and can be regenerated from dried material by simply exposing to a humidity level within the same range of 10–70% RH.

The better physical stability of the triflate salt could have practical implications, particularly with regard to analytical work. The resistance of the triflate monohydrate salt to adsorb excess water meant that the amount of water adsorbed by the solid during typical handling and weighing operations or during storage would be less of a concern compared to the perchlorate monohydrate salt, due to the tendency of the perchlorate salt to adsorb water even at humidity levels as low as 50% RH. If stored in a poorly sealed container, the water content of sodium perchlorate monohydrate salt would likely increase significantly over time, meaning that a given weight of material will contain more water and less sodium perchlorate than expected. This was not the case for sodium triflate monohydrate, provided humidity was below 70% RH. Thus, the triflate salt had the potential to reduce a source of weighing error which could have arisen from less than optimal storage conditions. This was an important practical consideration in RP-LC, because analyte retention times would be significantly affected by the amount of chaotropic additive in the mobile phase (Figure 2), and consequently predictable retention times of cationic analytes would only be possible if the amount of chaotropic salt in the mobile phase is carefully controlled.

Although the storage and handling properties of sodium triflate monohydrate may have offered some advantages over sodium perchlorate monohydrate, another practical consideration was the relative cost of the two salts. For the purchase of gram quantities of the materials, a substantially higher price for sodium triflate compared to sodium perchlorate, by a factor of approximately 10, was observed. Although the higher price would unlikely constitute a problem for industrial settings, it may be an issue in academic laboratories which are more sensitive to cost restraints.

Another potential difference between the perchloric and triflic acids was the chemical reactivity. It is known that perchloric acid and its salts can be explosive under certain conditions due to their oxidative nature, in contrast to non-oxidative triflic acid and its salts (24,26–28). However, it is important to note that per-

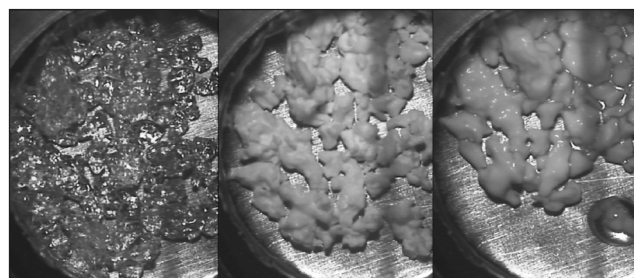


Figure 8. Magnified photographs of sodium perchlorate monohydrate sample during DVS analysis. Left, initial condition. Center, dry material after 16 h at 0% RH condition. Right, material showing onset of deliquescence after 6 h at 50% RH condition. Scale of photographs can be estimated from the size of the sample pan (8 mm diameter).

chloric acid or sodium perchlorate are hazardous only when in very concentrated solutions or when heated, and considering the low concentrations (< 1%) typically used in mobile phases, it appears unlikely that the use of perchloric acid or sodium perchlorate as an LC mobile phase additive is significantly more hazardous than the use of triflic acid or sodium triflate. Nevertheless, it should be kept in mind that spills of mobile phases containing perchloric acid or its salts could constitute a hazard if not cleaned up according to established guidelines (26), resulting in the possibility of forming a more concentrated residue of perchloric acid due to evaporation of solvent.

Conclusion

In this study, sodium triflate exhibited very similar retaining power of cationic analytes relative to perchlorate, based on the retention time of several cationic drugs when chromatographed on an RP-LC column using equimolar concentrations of the additives. However, analysis of the physical properties of sodium triflate and sodium perchlorate salts suggested that, in certain respects, sodium triflate salt may have superior handling properties compared to sodium perchlorate. Sodium triflate was supplied as anhydrous material, but could be quantitatively converted to a monohydrate by simply exposing to ambient laboratory conditions overnight. The resulting monohydrate was stable within the 10–70% RH range, and could be reversibly converted between anhydrous and monohydrate forms by manipulation of the humidity level. On the other hand, sodium perchlorate monohydrate was stable only under a very narrow RH range of 20–40%. At 50% RH or higher, excess water was adsorbed and deliquescence of the solid occurred. At 10% RH or lower, water was lost and the material became anhydrous. Conversion of the anhydrous material back to the monohydrate did not appear to be possible by manipulation of the humidity level.

Although both the triflate and perchlorate salts show very similar chaotropic effect in RP-LC the superior handling properties of the triflate monohydrate salt makes sodium triflate an attractive alternative to sodium perchlorate, and is worthy of serious consideration by RP-LC practitioners in the pharmaceutical industry.

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